

The research conundrum of acute appendicitis

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Despite specialization, virtually every surgeon has an opinion on the appendix and its inflammation. Appendectomy is learned early during training and it is estimated that over 300 000 patients in the USA and 50 000 in the UK undergo this operation every year. Notably, these patients are drawn from a larger population with 'suspected appendicitis' seen in primary care or in hospital. Clinical dogmas are passed on from master to apprentice, with each generation of surgeons creating their own era of myths and truths about this disease. Societal influences and the healthcare burden are considerable. A PubMed search of the term 'appendicitis' in May 2015 yielded over 20 000 articles, of which about one-third stem from the past decade alone. Although articles related to this worm-like organ fell just short of the number relating to another well investigated worm (*Caenorhabditis elegans* had 22 000 PubMed articles during the same period), any similarity in numbers does not equal advances in knowledge. *C. elegans* is frequently used as a model to further understanding in basic biology, whereas many publications on appendicitis are case reports, or institutional or personal series. Most studies are observational with few advances in scientific progress. No major journal dealing in basic or translational science has published a report on appendicitis in the past decade. There is little that represents new understanding of appendicitis in either specialist¹ or general medical² journals. Randomized trials are few and far between.

A historical focus on rapid diagnosis and early surgical removal, with acceptance of high negative appendectomy rates (over 20 per cent) in the belief that early removal would avoid perforation, prevailed for virtually the entire 20th century. Since then, early diagnostic laparoscopy, laparoscopic removal³, and debate over three holes *versus* one hole⁴ or no hole⁵ has been witnessed. Some 40 randomized trials have compared laparoscopic with open appendectomy, most of which are underpowered. Randomized trials comparing antibiotics with surgery remain few and inevitably contain inclusion criteria that limit generalizability. The increasing use of modern imaging techniques (ultrasonography, CT, MRI), societal needs for low negative appendectomy rates (below 5 per cent) and the introduction of non-operative management with antibiotics for simple acute appendicitis are drivers for change in the management of patients with suspected acute appendicitis.

Although there has been an evolution in management, no such progress seems evident in gaining a more complete understanding of the appendix, its role and what causes inflammation. No animal model has been reported in decades⁶, although some recent attempts have emerged albeit in an effort to understand the relationship between the appendix and inflammatory bowel disease^{7,8}. No 'omics' technology has advanced understanding of appendicitis, largely because it has not been used to address this research question. Newer investigation into the complexities of the

microbiome may be relevant, but the topic is unlikely to be in many surgeons' focused reading list⁹. There is no appendicitis 'awareness day' or coloured wristband, no funding agencies, nor famous 'appy' bloggers. Some would contend that there is no need either, as this vestigial organ does not bother the majority of humans (the estimated lifetime risk of developing appendicitis is only 7 per cent).

Although many patients with appendicitis can be diagnosed confidently from a thorough clinical history and examination, the pressure to perform imaging comes from the increased pressure on both emergency departments and hospitals in general to develop effective clinical pathways that result in short stays. Fear of litigation may also drive the need for imaging, as both diagnostic delay and misdiagnosis rank high in claims related to appendicitis¹⁰. Furthermore, current demands for precision in diagnosis no longer extend simply to a 'rule-in' or 'rule-out' diagnosis of appendicitis, but require the distinction between 'uncomplicated' and 'complicated' appendicitis to guide management. This drive towards compulsory imaging is not without consequences. It has been calculated that CT leads to an excessive exposure to radiation in a predominantly young population, and that the benefit of universal imaging is avoidance of 12 unnecessary appendectomies at the cost of one additional cancer death¹¹. As death is rare after appendectomy, exposure of young patients to radiation merits justification in terms of future cancer risk.

The move towards a non-operative approach to uncomplicated

appendicitis also raises issues related to the potential overuse of antibiotics. The pressure to restrict the use of antibiotics in order to reduce resistance patterns and secondary antibiotic-induced disease (such as *Clostridium difficile* colitis) is increasing. The ability to determine which patients and disease characteristics are most suited to a specific management strategy necessitates a better basic understanding of both patients and disease.

Advances in surgery imply progress, not merely innovation. In the context of appendicitis, the focus on novelty has prevailed over scientific knowledge in recent years. Technical innovation has not changed the course of disease, or enhanced understanding of who needs an operation. Some recent studies in *BJS*, however, suggest that some progress is being made. Clinically relevant precision in diagnosis has been described using an Appendicitis Inflammatory Response score to guide decision-making for suspected appendicitis¹². Although this observation would benefit from validation elsewhere, if more widely applied it could be used to reduce radiation exposure, particularly among younger patients. Another study¹³ used a combination of clinical and imaging criteria to separate uncomplicated from complicated appendicitis, achieving a 95 per cent negative predictive power for uncomplicated disease. If validated in external cohorts, this approach could inform the design of future trials.

Understanding the appendix and its role in inflammation is still limited. The protective role of appendectomy for ulcerative colitis with an increased risk of developing Crohn's disease is an inflammatory paradox, as yet unexplained. It seems surprising that appendectomy is associated with an increased risk of developing new-onset type II diabetes, as

reported in this journal¹⁴. With literally millions of appendectomies performed worldwide each year and the rising burden of diabetes as a global health problem, a better understanding of the role of the appendix in human health and disease is needed. It would seem that the neglected worm, so easily removed and often accused as the source of abdominal ailments, may indeed hold keys to other diseases. Perhaps only a subset of patients with inflamed appendices harbour the risk of developing severe inflammation, infection and abdominal sepsis, but why is this still not understood at a more sophisticated level? Only a more intense focus on basic science as well as translational and clinical research can provide the answers.

Disclosure

The author declares no conflict of interest

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